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ARTIFICIAL SWEETENERS AND LOWER URINARY TRACT CANCER: HOSPITAL VS. POPULATION CONTROLS

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In a case-control study conducted in 1978 in Detroit, Michigan, as part of the National Bladder Cancer Study, the proportions of artificial sweetener users in a hospital and a population control series were compared. The study was based on interviews with 305 hospital controls and 440 population controls, as well as 391 patients with transitional or squamous cell carcinoma of the lower urinary tract. The proportion of artificial sweetener users among all hospital controls was higher than that among population controls. Among male hospital controls, it was found that 44% had ever used artificial sweeteners, compared to 38% of the male population controls. For females, the corresponding proportions of artificial sweetener users were 55% and 42%. Thus, relative risks estimated using all hospital controls were lower than relative risks estimated using population controls. When controls hospitalized for obesity-related diseases were excluded from the hospital control group, the proportion of artificial sweetener users and the relative risks for males were identical to those estimated with population controls (relative risk = 1.1). These results suggest that restriction of the control group to those patients hospitalized for non-obesity related diseases is a satisfactory procedure for selecting a control group in hospital-based studies of the effects of artificial sweeteners. For females, little or no change in the proportion of artificial sweetener users or in the relative risks was observed after exclusion of controls hospitalized for obesity-related diseases. However, the number of female subjects was small, and the results noted for females may have been due to chance.

bladder neoplasms; sweetening agents; urinary tract

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This is a report of a case-control study of cancer of the lower urinary tract (bladder cancer) conducted in Detroit, Michigan. This study was part of the National Bladder Cancer Study (1), which was a population-based case-control study designed to evaluate the association between artificial sweeteners and the development of bladder cancer. The results of the national study indicated that artificial sweetener users had no overall increased risk of bladder cancer. At the time the study was initiated, the relation between artificial sweeteners and bladder cancer had been examined in five case-control studies (2–7). These studies differed with respect to the type of control group selected: in four studies (2–5), controls were chosen from patients in the same hospital as the cases, and, in the fifth study (6, 7), controls were drawn from the neighborhood of the cases. The results of the hospital-based studies (2–5) provided little or no evidence of an overall positive association between artificial sweetener use and bladder cancer risk, whereas the study based on neighborhood controls (6, 7) indicated a positive association for males.

These conflicting results generated a controversy regarding whether hospital controls constitute a valid control group in case-control studies of the effects of artificial sweeteners (7). Since conditions related to use of artificial sweeteners (such as diabetes and other endocrine and metabolic diseases, hypertension, myocardial infarction, and other cardiovascular diseases) are more highly prevalent in hospital patients than in the general population, the estimate of the artificial sweetener effect based on hospital controls might be biased. In the present study, we selected a hospital control series, in addition to the population control series selected for the national study. We compared the proportions of artificial sweetener users in these two control groups in order to determine the extent of this bias and ways in which it can be eliminated. One approach for eliminating such bias from hospital-based studies is to exclude controls hospitalized for conditions known or suspected of being related to the exposure under study (8–13). However, there has been little formal examination of the effect of such exclusion.

Materials and methods

Subjects

Cases. We attempted to identify all histologically confirmed cases of carcinoma (or papilloma not specified as benign) of the urinary bladder, renal pelvis, ureter, and urethra first diagnosed during a one-year period that began in December, 1977. Only cases that occurred in residents of the metropolitan Detroit area (Macomb, Oakland, and Wayne counties) between the ages of 21 and 84 years were considered eligible for the study.

Hospital controls. For reasons of practicality, we selected hospital controls at only 35 of the 60 hospitals participating in the study. These 35 hospitals contributed 87 per cent of the total cases identified for study. The proportion of artificial sweetener users among cases identified at these 35 hospitals was similar to that in the total case series (males, 37 per cent vs. 40 per cent; females, 58 per cent vs. 57 per cent). For this reason and because of the added precision gained by greater numbers, the total case series was included in the analysis. For each case identified at one of the 35 hospitals, a control was selected (irrespective of diagnosis) from the discharge lists of the same hospital. Cases and hospital controls were also matched for age (within five years), race, sex, and approximate date of discharge. To be eligible, the control had to be a resident of metropolitan Detroit.

Population controls. The population control series was drawn from the general

population of the study area. Cases and population controls were frequency matched for age (within five years) and sex. Approximately as many population controls as cases were selected. We chose population controls aged 21–64 years using a method of random digit dialing (14). First, 2368 households were selected at random from all Detroit residences with telephones to obtain the age and sex of every household member between the ages of 21 and 64 years. Of the households identified, 89 per cent gave a household census. Second, we selected a stratified random sample of population controls aged 21–64 years from the household censuses. The population control series aged 65–84 years consisted of a stratified random sample drawn from the Health Care Financing Administration's lists of the Detroit population over age 64 years.

Completeness of interviewing

Interviews were obtained for 445 cases (91 per cent of the total cases approached for interview), 538 population controls (91 per cent), and 347 hospital controls (89 per cent). Interviews were not obtained for 117 cases, 75 population controls, and 143 hospital controls for the reasons indicated in table 1.

The analysis was confined to white subjects because there were too few nonwhite subjects for satisfactory analysis. In addition, 14 cases, six hospital controls, and six population controls were considered ineligible for analysis for several reasons: the subject provided insufficient information to determine an accurate history of artificial sweetener use; the interview was judged by the interviewer to be unreliable; the case had a tumor not specified as transitional or squamous cell carcinoma; or the potential control had lower urinary tract cancer before the study period. A total of 391 cases, 305 hospital controls, and 440 population controls were included in the present analysis.

Data collection

Questionnaires were administered in person by a trained interviewer for most subjects. When this approach was not feasible, the interview was conducted on the telephone (for 35 cases, 51 hospital controls, and 18 population controls). When a subject was either too ill to be interviewed or had died, a family member or friend who knew the subject well was approached for a proxy interview.

The questionnaire was the same as that

TABLE 1

Numbers and percentages of cases of lower urinary tract cancer and controls according to interview outcome, Detroit, Michigan, 1978

	Cases		Total population controls		Total hospital controls	
	No.	%	No.	%	No.	%
Interviewed*	445	79	538	88	347	71
Dead	17	3	2	0	23	5
Disabled	18	3	4	1	26	5
Not located	15	3	16	2	26	5
Physician declined permission to interview patient	24	4	–	–	27	6
Refused to participate	43	8	53	9	41	8
Total identified	562	100	613	100	490	100

* Included interviews with proxy respondents for 45 cases, 16 population controls, and 46 hospital controls.

administered in all areas that participated in the National Bladder Cancer Study (1). To elicit detailed information on consumption of artificial sweeteners, the questionnaire included items on the use of table-top sweeteners, diet drinks, and diet foods. Information was also obtained on smoking, occupation, coffee consumption, residence, source of water, fluid intake, use of hair dyes, and specific illnesses (i.e., diabetes, bladder, and kidney conditions).

For each hospital control identified for study, all discharge diagnoses listed on the discharge summary were recorded. Discharge diagnoses were coded according to the Eighth Revision of the International Classification of Diseases, Adapted for Use in the United States (15). In the present analysis, we used only the primary discharge diagnosis, which was taken to be the reason for hospitalization. The reason for hospitalization of all hospital controls was reviewed by a physician, and controls hospitalized for conditions potentially related to obesity were identified. This review was conducted without knowledge of the subject's consumption of artificial sweeteners.

Analytic methods

The primary measure of exposure was the proportion of users of any form of artificial sweeteners (i.e., table-top sweeteners, diet drinks, or diet foods). In addition, all analyses were repeated considering each form of artificial sweetener separately. The measure of association between artificial sweetener consumption and the incidence rates of lower urinary tract cancer was the "relative risk" as estimated by the odds ratio. Adjusted relative risks were computed by the maximum likelihood method (16). Initially, the data were stratified by age, smoking, education, and body mass index (17). Adjustment for these factors had virtually no impact on the proportions of users or on the estimates of relative risk; thus, adjustments for these factors were not included in this presentation. In all comparisons, the unexposed group included only subjects who never used any form of artificial sweeteners. "Artificial sweetener use," as referred to in the present analysis, denotes exposure to one or more forms of artificial sweeteners. Artificial sweetener exposure after the starting date of the study was ignored.

Results

Proportion of artificial sweetener users

Table 2 indicates that the proportion of artificial sweetener users in the total hospital control group was higher than that in the population control group. For males, 44 per cent of hospital controls had ever used any form of artificial sweeteners compared to 38 per cent of population controls. For females, 55 per cent of hospital controls and 42 per cent of population controls had ever used any form of artificial sweeteners. A similar pattern was observed regardless of whether use of table-top sweeteners, diet drinks, or diet foods was examined.

We considered hospitalization for "obesity-related diseases" as the primary basis for exclusion of controls with diseases potentially related to artificial sweetener use. (Diagnoses of obesity-related diseases *incidental* to hospitalization were ignored.) Obesity-related diseases were defined as those diseases for which obesity is a risk factor or for which weight reduction may be recommended therapeutically. The specific diagnoses included in the obesity-related disease category are shown in table 3.

For males, 55 per cent of hospital controls with obesity-related diseases reported ever having used artificial sweeteners compared to 38 per cent of hospital controls without obesity-related diseases. In fact, the proportion of users was consistently higher among male hospital controls with obesity-related diseases than

TABLE 2

Numbers of controls and percentages of controls who ever used artificial sweeteners, by sex and type of control group, Detroit, Michigan, 1978

	Males			Females		
	Total population controls	Total hospital controls	Hospital controls without obesity-related diseases	Total population controls	Total hospital controls	Hospital controls without obesity-related diseases
Total no.	296	234	152	144	71	44
% who ever used:						
Any artificial sweeteners	38	44	38	42	55	55
Table-top sweeteners*	24	29	26	25	42	39
Diet drinks*	24	30	26	28	32	34
Diet foods*	13	16	11	14	18	21

* Subjects included in this category may have used other forms of artificial sweeteners.

among those without obesity-related diseases irrespective of the type of artificial sweetener considered. Table 2 shows that after males with obesity-related diseases were excluded from the hospital control group, the proportion of artificial sweetener users was identical to that observed among population controls (38 per cent). For each form of artificial sweetener, the proportion of users among male hospital controls without obesity-related diseases was also similar to the proportion observed among population controls.

For females, the proportion of users of any form of artificial sweeteners among hospital controls with obesity-related diseases was almost identical to that among hospital controls without such diseases (56 and 55 per cent, respectively). This finding was not consistent when we considered use by female hospital controls of each form of artificial sweetener separately. For table-top sweeteners, the proportion of users among hospital controls with obesity-related diseases was higher than that among those without such diseases (48 and 39 per cent, respectively). For diet drinks and diet foods, in contrast, the proportion of users among hospital controls with obesity-related diseases was lower than that among those without such diseases. However, table 2 indicates that the proportion of users among female hospital controls without obesity-related diseases was consistently higher than that among population controls regardless of whether we considered any use of artificial sweeteners or use of each form of sweetener.

We also compared total lifetime consumption of artificial sweeteners among all hospital and population controls. For both male and female artificial sweetener users, the amount used by hospital controls was similar to the amount used by population controls. Thus, the reported differences in artificial sweetener use between hospital and population controls were restricted to differences in ever/

TABLE 3

Numbers and percentages of controls hospitalized for obesity-related diseases, by primary diagnosis, Detroit, Michigan, 1978*

Diagnostic category	No.	%
Acute myocardial infarction	7	6.4
Other acute forms of ischemic heart disease	3	2.8
Chronic ischemic heart disease	32	29.4
Angina pectoris	3	2.8
Symptomatic heart disease	9	8.3
Other forms of heart disease	2	1.8
Cerebrovascular disease	12	11.0
Aortic aneurysm	2	1.8
Pain in chest	2	1.8
Vascular and cardiac surgery	2	1.8
Malignant neoplasm of the breast	2	1.8
Diabetes mellitus	4	3.7
Hypertensive disease	4	3.7
Arterial embolism and thrombosis	1	0.9
Phlebitis and thrombophlebitis	2	1.8
Varicose veins of lower extremities	1	0.9
Cholelithiasis	4	3.7
Other diseases of gallbladder and biliary ducts	4	3.7
Arthritis and rheumatism	5	4.6
Displacement of intervertebral disc	6	5.5
Congenital anomalies of musculoskeletal system	1	0.9
Surgery on joint structures	1	0.9
All obesity-related diseases	109	100.0

* Obesity-related diseases were defined as those diseases for which obesity is a risk factor or weight reduction may be recommended therapeutically.

never used artificial sweeteners rather than amount of artificial sweeteners used.

Relative risk associated with artificial sweetener use

For any use of artificial sweeteners and use of each form of sweetener, relative risks estimated using hospital controls were consistently lower than those estimated using population controls (table 4). Males who had ever used artificial sweeteners had a relative risk estimated as 0.9 using hospital controls and 1.1 using population controls. For females, the relative risk associated with artificial sweetener consumption was estimated as 1.1 using hospital controls and 1.8 using population controls.

For males, after exclusion of controls hospitalized for obesity-related diseases, relative risks estimated using hospital controls were similar to those estimated using population controls (table 4). Males who had ever used artificial sweeteners had a relative risk of 1.1 when the control group was either hospital controls without obesity-related diseases or population controls. Similar findings were also seen for table-top sweeteners, diet drinks, and diet foods.

Little or no change in the relative risks estimated for females was apparent after exclusion of controls hospitalized for obesity-related diseases (table 4). The relative risks estimated using hospital controls without obesity-related diseases were consistently lower than those estimated using population controls regardless of whether exposure was to total artificial sweeteners or to each form of

TABLE 4

Numbers of cases of lower urinary tract cancer and controls, and relative risks according to history of use of artificial sweeteners, Detroit, Michigan, 1978

Use of artificial sweeteners, by sex	Cases	Total population controls	RR*	Total hospital controls	RR*	Hospital controls without obesity-related diseases	RR*
Males							
Never used	182	183	1.0	132	1.0	95	1.0
Ever used	119	113	1.1	102	0.9	57	1.1
Table-top sweeteners†	83	72	1.2	67	0.9	39	1.1
Diet drinks†	83	70	1.2	70	0.9	39	1.1
Diet foods†	38	38	1.0	37	0.7	17	1.2
Females							
Never used	39	84	1.0	32	1.0	20	1.0
Ever used	51	60	1.8	39	1.1	24	1.1
Table-top sweeteners†	35	36	2.1	30	1.0	17	1.1
Diet drinks†	37	40	2.0	23	1.3	15	1.3
Diet foods†	20	20	2.2	13	1.3	9	1.1

* RR, crude relative risk.
† Subjects included in this category may have used other forms of artificial sweeteners.

sweetener. However, these relative risk estimates were based on small numbers and tended to be unstable.

DISCUSSION

This study was done to address a methodologic problem regarding procedures for selecting a control group in hospital-based studies of the effects of artificial sweeteners. The data presented here are only a fraction of the total data set from the National Bladder Cancer Study. Detailed results concerning the question of an overall association between artificial sweetener use and the risk of developing bladder cancer based on data from the National Bladder Cancer Study are discussed elsewhere (1).

Our findings indicate that the prevalence of artificial sweetener exposure among hospital patients is indeed higher than that in the source population for the cases. This bias was not eliminated by adjustment for body mass since hospital controls were not more obese than population controls. In fact, within individual body mass strata, the proportion of artificial sweetener users among hospital controls was higher than that among population controls. Thus, the difference in artificial sweetener exposure between hospital and population controls is not a function of body mass per se; rather, it is related to the high prevalence of obesity-related diseases among hospital controls. Many obesity-related diseases are illnesses for which weight reduction is routinely recommended, often leading to therapeutic intervention with artificial sweeteners.

For males, the high proportion of artificial sweetener users observed among all hospital controls was clearly due to the high proportion of users among controls hospitalized for obesity-related diseases. When controls hospitalized for obesity-related diseases were excluded from the control group, the proportion of artificial sweetener users and the relative risks for males were similar to those estimated using population controls. For females, in contrast, the observed proportion of artificial sweetener users among hospital controls was higher than that among population controls regardless of whether all hospital controls or only those without obesity-related diseases were considered. Exclusion of controls hospitalized for obesity-related diseases had little impact on the relative risks estimated for females; relative risks estimated using hospital controls remained lower than those estimated using population controls.

Three possible explanations for the findings noted for females are apparent: 1) *Chance*. The results observed for

females were based on small numbers of subjects and may have been due to chance. 2) *Reasons for use of artificial sweeteners.* It is conceivable that some unidentified correlate of hospitalization other than disease may be related to artificial sweetener use among females. If a high proportion of female hospital controls used artificial sweeteners for reasons unrelated to their illness, exclusion of controls on the basis of diagnosis would have little impact on the prevalence of artificial sweetener exposure in the female hospital control group. 3) *Recall bias in female controls.* The proportion of artificial sweetener users among female hospital controls without obesity-related diseases was almost identical to that among those with obesity-related diseases, and each of these proportions was higher than that among female population controls. These findings could have resulted from either the overreporting of artificial sweetener consumption by female hospital controls or, conversely, the underreporting of sweetener consumption by female population controls. It is our opinion, however, that either of the first two explanations is more plausible than the last since a sex-specific recall bias seems quite unlikely.

In conclusion, our results should not be interpreted as suggesting that hospital controls constitute an improper control group in case-control studies of the effects of artificial sweeteners. Rather, the results noted for males suggest that restriction of the control group to those patients hospitalized for non-obesity related diseases is a satisfactory procedure for selecting a hospital control group. This finding warrants consideration in future hospital-based studies of the effects of artificial sweeteners. Failure to exclude controls hospitalized for obesity-related diseases may result in biased estimation of the relative risks associated with use of artificial sweeteners. The magnitude of this bias will depend on two factors that may vary between studies done in different places or at different times: 1) the distribution of obesity-related diseases among the hospital controls, and 2) the relation of these diseases to artificial sweetener use.

The disparity between the findings noted for males and females in this study makes it somewhat difficult to draw general conclusions. If these differences are simply due to chance findings for the small group of females, as we believe, then the conclusions described above are appropriate. However, the differences in artificial sweetener use between female hospital and population controls may, in fact, be real and not due to the high prevalence of obesity-related diseases among female hospital controls. The use of hospital controls in estimating the effects of artificial sweeteners among females would then be inappropriate until the determinants of these differences could be identified.

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